(12) UK Patent Application (19) GB (11) 2 350 469 (13) A

(43) Date of A Publication 29.11.2000

(21) Application No 0012561.7

(22) Date of Filing 24.05.2000

(30) Priority Data
(31) 9911829 (32) 24.05.1999 (33) GB

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(51) INT CL[7]
G10H 1/00

(52) UK CL (Edition R)
G5J JESX

(56) Documents Cited
None

(58) Field of Search
UK CL (Edition R) G5J JER JESX
INT CL[7] G10H 1/00 3/00 5/00 7/00
Online: WPI, EPODOC, JAPIO

(54) Abstract Title
A method of producing audibly discernible sounds

(57) Means for producing an audibly discernable representation of a three dimensional structure such as a biological structure comprises a preliminary analysis of the structure to determine three dimensional positional coordinate data, processing this data to filter out large scale and small scale variations into successive sets of data, combining this data into a single sequence and generating audible sounds therefrom relating to the positional coordinate data. The biological structure represented are proteins whereby the CA carbon atoms of the amino acids of the proteins are analysed by x-ray crystallography to produce the data sets for generating the audible sounds.

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A METHOD OF PRODUCING AUDIBLY DISCERNIBLE SOUNDS

The present invention relates generally to a method for producing audibly discernible sounds, and particularly to a method in which the sounds are representative of complex structures.

In the representation of complex structures occupying three-dimensional space it has been conventional either to use stylised models of the structures, themselves occupying the three-dimensional space, or to represent the structures in two-dimensions with an appropriate representational convention by which the information concerning the third dimension is conveyed.

Each of these representational techniques has inherent drawbacks. Three-dimensional models, although they can be produced accurately, are not readily transportable nor are they indefinitely extendable, so that, for example, a highly complex structure may be limited to a representation of only a portion under immediate examination. Although two-dimensional representations are more readily portable, and can also be converted into a form suitable for display on a screen such as a computer screen, the necessity for a drawing convention to represent the third dimension results in a degree of imprecision and uncertainty in the accuracy of the representation. The present invention proposes a complete departure from conventional representational techniques by proposing to provide an audibly discernible representation of spatial information.

The present invention finds particular (but not exclusive) application in the

representation of naturally-occurring structures such as biological structures, especially proteins. Structure, pattern and form are inherent in naturally-occurring biological material, and these features may be drawn upon to provide parameters for audibly discernible representations. In the representation of spatial information in audible form the audible information may approximate to, or be considered as, music. Culture and musical tradition has resulted in the evolution of music consisting of references and structures often not consciously appreciated by the listener but nevertheless having an effect on the physiological perception of the music. Recent developments in digital computing have made available to musicians further means by which musical composition may be developed, and it is not unknown for a digital computer to be used as a compositional tool for developing new structures in music. This new type of music is sometimes called algorithmic, and such music, developed with computer process rules, may combine tonal and structural relationships which it would be difficult to calculate by traditional means.

The audible representation of biological structures such as proteins may, therefore, result in sounds which may be musical in their form. Proteins are biological macro molecules which are the fundamental building blocks in all life forms. Proteins are composed of a plurality of sub units, amino acids, which are arranged according to the individual amino acid properties to form a three dimensional molecule. It is recognised that music is defined by the intervals between notes rather than the absolute pitches of the notes and, correspondingly, proteins may be considered as being defined more by their overall patterns than by their absolute or primary sequences. Proteins structures may be considered to comprise four mains elements or levels of complexity, namely a

primary structure which is the linear order in which the amino acid sub units occur. A secondary and a tertiary structure determined by the properties of these amino acids which give rise to structural features referred to by biologists as loops, turns, alpha helices and beta strands or beta sheets depending on the spatial arrangements of the sub units in the linear sequence. Quaternary structures are recognisable as the quaternary structure is the broadest structural level concerned with the arrangement of individual protein "blocks" which fit together to form the final protein molecule.

At the primary level, alpha helices are uniform coil-like structures in which the functional groups or R-groups of the amino acid project outward from the helix axis. On the other hand secondary structures known as beta strands fold back and forth with individual amino acid R-groups projecting from the folded chain on alternate sides. Different beta strands may be aligned with one another, adjacent strands forming weak bonds which connect them into what are called beta-sheets. Also at the secondary/tertiary level regions of the molecule referred to as "turns" follow a different directional path and are commonly found connecting two regions of an alpha helix or beta strands. These are structures spanning both the secondary and tertiary level in that the folding patterns of the secondary structures are combined to produce the overall tertiary structure of a protein. Information concerning the relationship of these features is usually considered at a visual level and represented visually. The present invention provides an alternative means of representation allowing other senses to be involved.

According to one aspect of the present invention, therefore, a method of producing an

audibly discernible representation of a three dimensional structure comprises the steps of:

generating numerical information concerning the spatial position of identifiable components of the structure from analysis of the structure,

converting the numerical information into a derived digital signal by forming moving averages of the numerical information,

subjecting the derived digital signal to a conversion from the three-dimensional value to produce a signal having a scalar value representing at least one of the properties of a audibly discernible sound, and

generating a sound having that or those properties.

At a fundamental level it may be considered that each positional coordinate representing the presence of a feature or structural element of the structure may be allocated a unique discernible sound. It is of course important that the same sound is repeatably produced by the same feature, but it is not essential that only one feature produce that sound.applied to the representation of a naturally occurring structure, such as a protein the analysis may be performed by x-ray crystallography to determine the relative locations of the amino acids of which the protein is composed. In its application to other structures, however, different analysis techniques may be used on order to generate the raw positional data and, of course, the coordinate information may represent the positions of other significant elements in the structure. In an engineering structure, for example, the positional coordinates may represent the nodes in a load-bearing assembly and/or the stresses applied to elements of a structure during operation or when performing its function. For example, the stresses exerted on an

element of a building may be represented by pitch, variation of which represents increases in the stress so that dynamic variation of the stress pattern can be represented audibly which enables a plurality of different signals to be perceived simultaneously even in a structure in which, with a traditional visual representation, certain components may be masked or covered by others and therefore not visible.

In the representation of structures such as proteins the resultant data of the x-ray crystallography analysis may comprise a set of positional coordinates representing the relative positions of at least some of the atoms of the amino acids of the protein. In particular the positional coordinate data may represent the three dimensional positions in space, with respect to a given frame of reference, of the CA carbon atoms of the amino acids of the protein.

Although individual unique sounds may be generated these sounds may not necessarily be represented by individual musical notes, but could be other detectable sounds such as chords or discordant sounds.

In the performance of the method of the invention the said moving averages comprise at least a first moving average of the value of the positional coordinate data scanned over successive groups of carbon atoms to provide an approximate representation of the secondary structure of the amino acids in the protein.

Likewise, a second moving average of the values of the first moving average may be taken over a range of values thereof greater than the range used to form the first

moving average. This second moving average provides a further degree of "smoothing" to act effectively to filter out the smaller scale variations, without completely excluding larger scale variations.

Further sequences of digital signals may be derived from the said first and second moving averages, for example by determining the differences between the first moving average and the positional coordinate data, whereby to provide a digital data signal in which larger scale variations are not present and smaller scale variations are amplified.

The second further sequences of digital signals may be derived from the first and second moving averages by determining the differences between the first and second moving averages whereby, in effect, to act as a mid-frequency filter on the data.

The method may include deriving a third further sequence of digital signals by normalising the second moving average values about a selected origin to represent the large scale features of the positional coordinate data stream. This, effectively, acts as a low frequency filter to produce signal dependent on the large scale features.

The said first, second and third further sequences of digital signals may each be multiplied by a respective weighting factor and summed to produce a single sequence of averaged and processed three dimensional coordinate values which are then mapped onto a sequence of one-dimensional values. This may be achieved via a three-dimensional wave form generated by spectral synthesis, using a fourier synthesis technique, or by other techniques which provide a repeatable mapping of a three-

dimensional point onto a one-dimensional point which can be interpreted as a musical parameter. A simple example might be to sum together the three coordinate values to get a single one-dimensional value.

The one-dimensional value may be pitch or volume and other means may be provided for varying the attack and decay of the sound in order to generate musical notes.

The present invention also comprehends a method of producing an audibly discernible representation of a three-dimensional structure in which the identification of the details of secondary structures in the positional coordinate data is obtained by means of a filter.

In another aspect of the invention a method of producing audibly recognisable sounds representing respective amino acids in a protein structure comprises the steps of: subjecting the protein structure to an x-ray crystallography analysis to produce a series of raw data signals representing the three-dimensional positional coordinates of the CA carbon atoms of the amino acids of which the protein is composed; filtering the said raw data signals to generate a plurality of derived moving averages thereof whereby to filter out large and small scale variations respectively; generating from the derived moving averages a composite signal including weighted moving averages as components thereof; and generating from the said composite signal an audible signal in which each amino acid is represented by an identifiable musical note.

The present invention may be embodied in apparatus including visual display means by

which the raw data positional coordinate signals may be displayed graphically in synchronism with the audible output signals such that visual and aural correspondence is discernible.

The present invention also comprehends apparatus for producing an audibly discernible representation of a three-dimensional structure, comprising:

- means for analysing numerical information to generate representations of the position of identifiable components thereof;
- means for forming moving averages of the said numerical information,
- means for converting the moving averages of the numerical information into scalar values, and
- means for allocating pitch or volume values to the said scalar values to generate audible sounds related to the structure.

Various examples of the invention will now be more particularly described.

Example 1: for the generation of musical notes representing the individual amino acids of a protein structure, each x, y and z positional coordinate of the CA carbon atom from each amino acid in an original protein sequence S0 derived from x-ray crystallography analysis is processed twice, once to extract a first moving average S1, calculated by averaging the values of the sequence S0 over a range of five amino acids, and then a second time to extract a second moving average S2 calculated by averaging the values of the moving average S1 over a range of twenty five amino acids. The first moving average represents the secondary structure of the protein and the second

moving average represent the tertiary structure.

From these three digital data streams S 50, 51, 52 may be derived three further sequences as follows:

1. S0-1 is calculated by subtracting the first moving average S1 from the original three dimensional data S0. This has the effect of emphasising the small twists and turns of the protein and of masking the larger scale curves over the protein structure as a whole. This in effect acts as a high frequency filter on the three-dimensional structure of the protein and highlights the spiral shape of the alpha helices. By subtracting the first moving average from the original data all the short-term fluctuations are maintained within the structure of the alpha helices without interference from larger scale changes. By mapping this to pitch variation an accurate sonic representation of the alpha helices is obtained. This mapping results in the generation of sequences of arpeggios when the alpha helices are traversed, and the same or a slightly varying note is heard when the beta sheets are traversed. This latter results from the fact that a beta sheet contains few small-scale changes.

S1-2 is created by subtracting the second moving average from the first moving average. This has the effect of amplifying the medium sized turns of the protein whilst attenuating the higher frequency alpha helix turns and the lower frequency large scale curves. This process acts as a medium frequency filter on the three-dimensional structure.

Finally, S2-3 is derived by calculating the mean position of all the amino acids in the

raw data S0 to create a second moving average by subtracting this mean from each value of a coordinate for an amino acid in the moving average S2. The resulting sequence S2-3 is essentially identical to the sequence S2 but is normalised about a central zero origin point. This sequence represents the larger scale curves of the original three-dimensional protein structure, effectively acting as a low frequency filter.

Weighting factors are then applied to each sequence and the weighted sequences summed to give a final sequence ST = a (S0-1) + b(S1-2) + c (S2-3). The magnitude of the weighting factor a determines the proportion of the high frequency component of the protein in the final sequence ST whilst b and c determine the mid frequency and low frequency component.

The sequence ST is than mapped onto musical parameters such as pitch via a three-dimensional waveform generated by three-dimensional spectral synthesis, thus creating sequences of notes which express visual features in musical form. The waveform maps a three-dimensional coordinate value onto a one-dimensional value, that is the value of that point in the waveform. The three dimensional input values are a sequence of coordinate values from ST and the output is a sequence of one-dimensional values which are interpreted as notes in musical scales or dynamic levels (volume). This mapping may be achieved as follows. First a random number (ranging from 5 to 20 or more) of vectors are provided which reside in a 2-dimensional frequency-space (the frequency-space is the spectral analog to the final 2 dimensional landscape). Each vector has a randomly determined position in this frequency-space and has a randomly determined phase and magnitude associated with it (represented by a complex number).

For mathematical reasons, there must also exist for each vector a 'mirror' vector with the same vector location but having a complex number associated with it that is a complex conjugate of the original vector's complex number. Therefore there must always be an even number of these vectors.

Once these vectors with their associated complex numbers have been generated it is a simple process of fourier synthesis so that given a 2-dimensional coordinate in cartesian space, one can sum the contributions of each vector (at the cartesian coordinate) to end up with a scalar (1-dimensional) value which can be interpreted as a height value. Details are given by D. Saupe. Since the resulting "landscape" is constructed from a combination of waves, for a small list of vectors it has the property that two points close to each other in 2-dimensions have similar resulting height values (i.e. mathematically speaking, the landscape is continuously differentiable everywhere.

This process is extended to 3-dimensions by generating a list of 3-dimensional vectors in frequency –space. When given a point in 3-dimensional cartesian space, these vectors can be summed using complex arithmetic to provide a 1-dimensional scalar value. This allows a 3-dimensional coordinate (i.e. 3-dimensional position of a CA atom after the moving average process) to be turned into a 1-dimensional scalar value. In an analogous way to the 2-dimensional synthesis, two points close to each other in 3-dimensional cartesian-space will have close 1-dimensional results from the mapping. This means that close 3-dimensional positions will have close (audibly related) pitch, amplitude or other such musical value.

Whilst this invention may make use of a fourier synthesis technique, fourier synthesis by such is not new, and this invention includes the use of any other method of mapping a 3-dimensional point, for example derived from filters or moving averages of x-ray crystallography data to a 1-dimensional point which can be interpreted in a musical fashion. A simple example might be simply to sum together the x, y, and z values of the 3-dimensional coordinate to get a single 1-dimensional value. Another alternative in the specific case of proteins may be to use the coordinates of the second moving average as an "axis" and to calculate "angular" offsets of the original data from that axis. As the alpha helix twists around a sequence of angles averaging around 360° may then be derived.

This output is then written to a MIDI text file for conversion into music or a layer in a musical arrangement using known MIDI music software to produce complex multi timbral musical pieces containing melodies reflecting the large-scale tertiary structures or small repetitive arpeggios expressing the structural nature of the alpha helices.

Example 2: for the production of a musical representation of a protein. This follows the same basic method as described in relation to example 1 above, with the addition of tempo, rhythm and key changes derived from the x-ray crystallography coordinate data.

In this example positions in the original data sequence are determined where the musical parameter changes are to take place corresponding to visual transmission points in the secondary structure of the protein, for example where an alpha helix, a

beta sheet, a loop or a turn begins or ends.

The secondary structure details are identified using a filter. This filter outputs secondary structure features from an input comprising the three-dimensional data. Two filter techniques may be used in the identification of the secondary structures, namely:

Filter technique 1. The three dimensional distance of each CA carbon atom is taken from the mean position of the CA carbon atoms of a particular section of the protein. The filter moves a window containing data covering approximately 10 CA carbon atoms for different amino acids along a section of the crystallography data looking at the distance of each CA carbon atom from the mean value of all the carbon atoms in the current window. From these distances it is possible to determine the likelihood of the current window containing data from an alpha helix or a beta sheet. The termination points of these features may thus be identified.

Filter technique 2. In this technique matched filters are used with parameters tuned to those found in protein alpha helices and beta strands and the like. For example, alpha helices will have an approximate pitch of 4.6 angstrom units, beta sheets will have an approximate pitch of 13.5 angstrom units.

Example 3. This example may be embodied in a model giving participants the opportunity to create their own pieces of music from a range of onscreen three dimensional proteins. The three dimensional x-ray crystallography x, y, z coordinate data is used as the basis for an animated display of the progress of the generated music

along the physical structure of the proteins as displayed graphically on a computer screen. By choosing from a selection of moving average operations the user can see how the chosen proteins are converted into musical sounds. The weightings a, b, c of example 1 may be made available to the user for selection, and their combination by the computer then results in a sequence of notes.

Each note, corresponding to a specific amino acid in the display, is then sounded with the amino acid on the display, with the visual representation of the protein being highlighted simultaneously whereby to demonstrate and emphasise the correspondence between the musical notes and the protein sequences.

Example 4: a display booth or exhibition kiosk may be equipped with an interactive touch screen computer system containing both the audio and visual components described in relation to examples 1 and 3. The screen may display graphics generated using a graphics processor depicting a traverse through the biological material of a plant, animal, insect, fungal, bacteria, yeast or human "landscape". The protein molecules are used to derive musical sounds identifying the proteins. This may also have an educational value in enabling aural recognition of proteins.

Example 5. Another educational application may be developed as a three dimensional tactile model of a protein containing a plurality of switches connected to a computer system whereby the display of an audio visual information device may be influenced. On touching a particular amino acid (that is operating the associated switch) the amino acid on the display screen would be highlighted and the corresponding note, chord or

other musical sound representing this amino acid generated for the user to hear.

The present invention thus expands and crosses the boundaries between science and art, enabling new approaches to understanding biological structure to be achieved as well as the generation of music for educational or purely entertainment purposes. Use of this invention in protein homology modelling, where fast and easily recognisable differences in proteins of similar structure are required, may be developed as there is a currently unfulfilled demand for such a tool in this widely used research technique.

Protein-derived music may be of therapeutic interest in the treatment of conditions currently treated using music therapy. It is believed that such specialised music may offer a focused and precise application which optimises and hence is more cost effective than, known music therapies utilising music derived from other sources. Protein-derived music may be used to strengthen mind-body connections. Likewise, protein-derived music may be used for studying and modelling protein sequence data, complementing existing techniques which have wide application in drug design. Since alpha helices, beta strands and turns each have characteristic combinations of hydrophobic and hydrophilic amino acids, different structural categories of proteins, which combine these secondary elements in different ways, also have different musical characteristics. The sounds generated therefrom may therefore be used effectively in the discrimination and demonstration of different protein types.

Protein music may also be used in sequence alignment and structural homology determination as structural homology may be heard when it might not easily be

perceived visually.

CLAIMS

1. A method of producing an audibly discernible representation of a three dimensional structure, comprising the steps of generating numerical information concerning the spatial positions of identifiable components of the structure from analysis of the structure, converting the numerical information into a derived digital signal by forming moving averages of the numerical information, subjecting the derived digital signals to conversion from a three dimensional value to produce a signal having a scalar value representing at least one of the properties of an audibly discernible sound, and generating a sound having that or those properties.

2. A method as claimed in claim 1, in which the structure is a protein and the analysis of the structure is performed by x-ray crystallography to determine the relative locations of the amino acids of which the protein is composed.

3. A method as claimed in claim 2, in which the results of the x-ray crystallography analysis comprises a set of position coordinates representing the relative positions of at least some of the atoms of the amino acids of the protein.

4. A method as claimed in claim 3, in which the position coordinate data represents the three dimensional position in space, with respect to a given frame of reference, of a carbon atom of the amino acids of the protein.

5. A method as claimed in any preceding claims, in which the said moving averages comprise at least a first moving average of the value of positional coordinate data scanned over successive groups of carbon atoms to provide an approximate representation of the secondary structure of the amino acids of the protein.

6. A method as claimed in claim 5, in which a second moving average of values of the first moving average is taken over a range of values thereof greater than the range used to form the first moving average.

7. A method as claimed in claim 6, in which there is formed a first further sequence of digital signals derived from said first and second moving averages by determining the difference between the first moving average and the positional coordinate data, whereby to provide a digital data signal in which larger scale variations are not present and smaller scale variations are amplified.

8. A method as claimed in claim 6 and claim 7, in which a second further sequence of digital signals are derived from the first and second moving averages by determining the difference between the first and second moving averages whereby in effect to act as a mid-frequency filter on the data.

9. A method as claimed in any of the claims 6 to 8, in which a third further sequence of digital signals is derived by normalising the second moving average values about a selected origin to represent the large scale features of the positional

coordinate data stream, acting effectively as a low frequency filter.

10. A method as claimed in Claim 9, in which the said first, second and third further sequences of digital signals are each multiplied by a respective weighting factor (a, b, c) and summarised to produce a single sequence (ST) averaged and processed three-dimensional coordinate values which are then mapped onto a sequence of one-dimensional values via a three-dimensional waveform generated by spectral synthesis.

11. A method as claimed in Claim 10, in which the one-dimensional value is pitch.

12. A method as claimed in Claim 11, in which the pitch signal represents a musical chord or a single note.

13. A method as claimed in Claim 10, in which the one-dimensional value is volume.

14. A method as claimed in any preceding claim, in which the identification of the details of secondary structures in the positional coordinate data is obtained by means of a filter.

15. A method of producing audibly recognisable sounds representing respective amino acids in a protein structure, comprising the steps of: subjecting the protein

structure to an x-ray crystallography analysis to produce a series of raw data signals representing the three-dimensional positional coordinates of the CA carbon atoms of the amino acids of which the protein is composed; filtering the said raw data signals to generate a plurality of derived moving averages thereof whereby to filter out large and small scale variations respectively; generating from the derived moving averages a composite signal including weighted moving averages as components thereof; and generating from the said composite signal an audible signal in which each amino acid is represented by an identifiable musical note.

16. A method as claimed in Claim 15, in which the raw data positional coordinate signals are also displayed graphically on a display screen in sychronisation with the audible output signals such that visual and aural correspondence is discernible.

17. Apparatus for producing an audibly discernible representation of a three-dimensional structure, comprising:

- means for analysing numerical information to generate representations of the position of identifiable components thereof;
- means for forming moving averages of the said numerical information,
- means for converting the moving averages of the numerical information into scalar values, and
- means for allocating pitch or volume values to the said scalar values to generate audible sounds related to the structure.

18. Apparatus as claimed in Claim 17, in which there are further provided means for displaying a two-dimensional visual representation of a three-dimensional structure, an interface with a user to allow selections of identifiable components of the structure to be made, and means for visually correlating the audible sounds produced by the apparatus with the displayed components.

19. Apparatus as claimed in Claim 18, further comprising means for identifying a plurality of components of a structure in sequence and generating a sequence of sounds in correspondence therewith.

20. Apparatus as claimed in Claim 17, further including a three-dimensional model of the structure, at least some of the said identifiable components thereof having associated switching means operable by a user in making selections of the sounds to be generated by the apparatus.

INVESTOR IN PEOPLE

Application No: GB 0012561.7 22 **Examiner:** Simon Colcombe
Claims searched: 1, 17 **Date of search:** 24 August 2000

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.R): G5J (JER, JESX)

Int Cl (Ed.7): G10H 1/00, 3/00, 5/00, 7/00

Other: Online: WPI, EPODOC, JAPIO

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	NONE	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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